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Effectiveness of two psychological interventions for prevention and management of pain, emotional regulation and promotion of quality of life among people with Haemophilia (PSY-HaEMOPEQ): study protocol for a single-center prospective randomized controlled trial

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ABSTRACT

Introduction: Haemophilia is a bleeding disorder associated with significant pain, emotional distress, quality of life (QoL) impairment and considerable healthcare costs. Psychosocial health and effective pain management are considered essential endpoints for optimal Haemophilia care, but there is a significant gap in evidence-based treatments targeting these outcomes in people with Haemophilia (PWH). Psychological interventions are cost-effective in promoting emotional well-being, QoL and pain control, though these have been scarcely used in Haemophilia field. This investigation aims to evaluate the effectiveness of two psychological interventions for prevention and management of pain, emotional regulation and promotion of QoL in PWH.

Methods and Analysis: This is a single-center parallel randomized controlled trial conducted at a European Haemophilia Comprehensive Care Center in Portugal, with five assessment points: baseline (T0), post-intervention (T1), 3 (T2), 6 (T3) and 12 (T4) months follow-up. Eligible adult males, with moderate or severe Haemophilia A or B will be randomized to experimental (EG) or control (CG) group. Intervention is either Cognitive-Behavioral Therapy (EG1) or Hypnosis (EG2), both consisting of four weakly sessions following standardized scripts delivered by trained psychologists. Randomization will be computer generated and allocation concealment will be guaranteed. Patients in the EG will be blind to type of intervention and outcome assessors will be blind to EG/CG allocation. Main outcomes are pain and Haemophilia-related QoL and secondary outcomes include clinical (factor replacement consumption, joint bleeding episodes, analgesic intake) and psychological (pain coping strategies, anxiety, depression, illness perceptions) variables, functional assessment of the joints, inflammatory biomarkers (cytokines, hs-CRP) and WBC count.

Ethics and dissemination: This study was approved by the competent authorities and all procedures will comply with international ethical guidelines for clinical studies involving humans. Written informed consent will be obtained from all participants. The dissemination plan includes peer-reviewed scientific publications, conference participation and web and media coverage.

Trial registration number: NCT02870452

Strengths and Limitations

- Haemophilia is a bleeding disorder associated with significant pain evolving to a chronic state, decreased QoL and considerable healthcare costs.
- This investigation will contribute to fill the gap on literature analyzing the effectiveness of psychological interventions for people with Haemophilia.
- Participants will be randomly allocated to the groups and the intervention providers will be assigned to each group according to their expertise in delivering the intervention (expertise-based RCT).
- Specific measures will be taken to limit bias, like blinded outcome assessment, standardization of intervention delivery and collection of concomitant treatment.
- This RCT is a single-center study, limiting the generalizability of findings.

I. INTRODUCTION

1. Background and Rational

Haemophilia is an inherited X-linked bleeding disorder caused by a deficiency in coagulation factor VIII (Haemophilia A) or IX (Haemophilia B). Due to this deficit in coagulation factor, the main clinical manifestation of Haemophilia is an increased bleeding tendency, either spontaneous or related to trauma or surgery. Spontaneous bleeding episodes occur mainly in the joints (hemarthrosis) and, if recurrent, lead to persistent joint damage and development of chronic joint arthropathy (hemophilic arthropathy).[1] Severity of Haemophilia is classified according to clotting factor level, being defined as mild (clotting factor between 5%-40% of normal), moderate (1% to 5% of normal clotting factor) or severe (clotting factor level under 1% of normal), which generally correlates to a correspondent increase in bleeding frequency.[2]

Given the clinical presentation of Haemophilia, the main goal of care is prevention and treatment of bleeds, which is mainly achieved through different modalities of factor replacement therapy. However, recent guidelines have also highlighted the importance of considering psychosocial health and quality of life (QoL) as important outcomes for optimal care among people with Haemophilia (PWH).[3,4] In fact, PWH have particular psychological and social needs related to Haemophilia-specific threats and challenges, such as pain and daily living restrictions,[5] which impact significantly on QoL.[6] Therefore, the focus of current Haemophilia management practice is not only to minimize joint disease but also to simultaneously increase QoL.[7]

In this context, a very relevant issue is pain, which is a common, highly debilitating feature of Haemophilia that has been related with decreased QoL.[8] PWH experience acute pain during joint bleeds, but might also report chronic pain resulting from hemophilic arthropathy. On a recent 10 country survey, chronic pain related to Haemophilia was reported by 38% of the respondents, highlighting the high prevalence of this condition among PWH.[4] Nevertheless, patient reports also account for sub-optimal pain management, with 33 to 39% of patients in the United States and Europe reporting dissatisfaction with current pain treatment.[4,9-11] This question is such an important issue that, in a very clearheaded editorial, Humphries and Kessler[12] emphasize that the improvement of pain assessment, prevention and control is a key endpoint in the development of future treatments for PWH. In sum, pain control should be a priority in Haemophilia treatment,[12] focusing not only on chronic pain management, but also on its prevention, as recommended by international guidelines, which state that non-pharmacological treatments, such as psychological interventions, should be considered for both these purposes.[8,9] However, despite well-established recommendations, there is still a scarcity of evidence-based treatment guidelines for Haemophilia pain management. This is one important limitation to treatment progress in this field, justifying the need to conduct robust intervention-type investigations in this population.[8]

Another noteworthy issue is that psychological or psychiatric conditions are reported by 47% of PWH, with 29% relating these symptoms to Haemophilia.[4] This is even more relevant considering that psychological factors can influence both pain experience and QoL in PWH.[11] Interestingly, Cassis and colleagues[6] state that variations in QoL are better explained by psychosocial, rather than clinical predictors. Since the former are potentially modifiable through psychological interventions, there is a recognized need to design interventions targeting social and psychological aspects of PWH.[13]

Indeed, psychological interventions have been proven to be effective in a broad range of disorders and illnesses.[14-17]Although a few former works have focused on psychological interventions in Haemophilia, showing positive and promising results,[18-24] it is somewhat surprising the lack of recent papers exploring this issue, despite the recommendations and guidelines that emphasize their relevance. In those publications, a blend of psychological techniques was applied, with particular emphasis on Hypnosis.[18,19,23,24] In fact, there is considerable evidence for the effectiveness of Hypnosis as an empirically supported clinical intervention in managing symptoms such as pain,[25-34] and also in promoting psychological well-

being across a variety of illnesses and disorders.[35-42] Among PWH, studies have shown that Hypnosis can contribute not only to control pain, but also to reduce frequency and severity of bleedings and factor consumption.[18,19,23] Concurrently, by promoting better disease management, Hypnosis can contribute to better coping and less distress.[23]

Besides Hypnosis, Cognitive-Behavioral Therapy is another psychological strategy commonly used in healthcare contexts. This has been the gold standard of psychological intervention, with recognized effectiveness in reducing negative emotions such as anxiety and depression, as well as in managing pain and promoting QoL in chronic disease.[14,16,43-47] Nevertheless, and to the best of our knowledge, it was never fully applied to Haemophilia field.

In sum, and despite the shortage of studies focused on psychological interventions in Haemophilia, these are recognized as complementary non-pharmacologic therapies and as a valuable resource to expand Haemophilia care and potentially maximize treatment outcomes, promoting QoL and emotional well-being and improving symptoms management.[11,13]

Another relevant issue in the field of Haemophilia concerns inflammatory biomarkers, such as cytokines and high-sensitivity C-reactive protein (hs-CRP), given their recognized role in inflammatory and degenerative processes that are related to the development of hemophilic arthropathy.[48] For instance, pro-inflammatory (*e.g.* IL-6, IL-1β, TNF-α) and anti-inflammatory (*e.g.* IL-10) cytokines have been implicated in the pathophysiology of hemophilic arthropathy, joint pain-associated nociceptive pathways and inhibitor development.[48-55] In addition, these biomarkers have also been shown to be correlates of psychological variables and, therefore, physiological approaches could support the potential efficacy of psychological interventions on disease and pain control.[56-58]

This is particularly relevant in light of the attention being given to psychosocial health in Haemophilia, which has been advocated as a priority in the improvement of health status and QoL in PWH.[4,59] To this purpose, it is recommended that comprehensive care teams should be multidisciplinary and include a psychosocial expert, who can provide complete assessment of psychosocial status and contribute to an integrated disease management plan.[3] Globally, integrated care models are preferred over non-integrated care models. However, there is still some uncertainty concerning which aspects of care might improve Haemophilia management and patient outcomes, and what is the ideal composition of Haemophilia care services.[60] Thus, there is an important gap between the need to clarify these issues and the lack of recent studies analyzing psychological interventions for PWH. This, added to the psychosocial impact

of Haemophilia discussed above, validates the need to advance research in this field, namely through the planning and implementation of clinical randomized controlled trials that test the effectiveness of distinct psychological interventions. In addition, it is noteworthy that, despite pain being recognized as an important consequence of bleeding disorders, it has not been taken into account in most clinical trials of Haemophilia.[12]

The current study protocol points to an innovative research that can contribute to better understand the impact and potential benefits of psychological interventions in Haemophilia care setting. Given the negative impact of Haemophilia on individual QoL and the associated healthcare costs, it is mandatory to evaluate the effectiveness of theoretically grounded psychological interventions in this field.

2. Objective

The primary objective of this study is to evaluate the relative effectiveness of two psychological interventions, Cognitive-Behavioral Therapy and Hypnosis, in order to prevent and manage pain, promote emotional regulation and improve QoL, among Portuguese PWH.

II. METHODS

1. Trial Design

The design of this study follows the recommendations of Yates and colleagues[61] concerning psychological trials for pain, and reporting of the study results will follow CONSORT guidelines for trials of non-pharmacological interventions.[62]

This is a single-center three arm parallel prospective randomized controlled trial (RCT), with one control group (CG) and two experimental groups (EG): Cognitive-Behavioral Therapy (CBT) and Hypnosis (HyP), using an expertise-based RCT design. Participants in both groups will be followed longitudinally, in five time assessment points:

T0: Baseline assessment (pre-intervention, before randomization)

T1: Post-test assessment (1 week after intervention)

T2: Follow-up assessment 1 (3 months after intervention)

T3: Follow-up assessment 2 (6 months after intervention)

T4: Follow-up assessment 3 (12 months after intervention)

2. Participants and Procedures

According to sample size calculation, 66 patients will enter the study. Estimations were made using G*Power 3.1.9 and considering the following assumptions: to perform a one-way ANOVA with fixed effects, large effect size (f =0.4), significance level (α – type I error) of 0.05 and statistical power (1-β – type II error) of 0.80.

Participants will be recruited at the European Haemophilia Comprehensive Care Center of São João Hospital Center, in Porto, Portugal. Eligible patients will be identified by the clinicians of the Haemophilia Centre and invited to participate if they comply with the following inclusion criteria:

a) Male gender;
b) Age ≥ 18;
c) Diagnosis of moderate or severe Haemophilia A or B, with or without inhibitors;
d) Diagnostic of hemophilic arthropathy in at least one joint;
e) Chronic pain;
f) Presence of anxiety or depressive symptoms (HADS ≥ 11);
g) Ability to consent voluntary participation to the study;
h) Ability to read and write;

The exclusion criteria are:

a) Severe and debilitating neurologic conditions (e.g. dementia);
b) Severe psychiatric conditions (e.g. schizophrenia);
c) Currently undergoing any form of psychotherapy
d) Unavailability to commit to four weekly sessions

Patients willing to enroll will be referred to the investigators, who will describe and explain the study's objectives and interventions and clarify any concern or doubt, emphasizing confidentiality and voluntary nature of participation. After acceptance, patients sign the informed consent and baseline assessment is performed (T0). After baseline assessment, participants are randomly assigned to one of the three groups (CBT, HyP or CG) and, for patients in CBT and HyP groups, four weekly individual intervention sessions are scheduled. On the fifth week, all the patients are assessed for post-test assessment (T1). Follow-up assessments will take place at 3 (T2), 6 (T3) and 12 (T4) months after intervention ending for all participants (CBT, HyP and CG). Participant timeline for enrolment, intervention and assessment points is schematized in Figure 1.

3. Randomization and Allocation

Randomization procedures will follow a stratified blocked randomization process using a computerized random sequence generator. In order to control for potential confounding effects, stratification will be done by Haemophilia severity. The generated sequence will be concealed and patient allocation will not be revealed until official enrollment, after consent is given and baseline assessment is completed. One of a series of consecutively numbered sealed opaque envelopes with group allocation will be opened at this moment and revealed to the patient. Due to obvious differences in procedure, blinding of the patients to intervention *vs*. control group is impossible. However, blinding to the type of psychological intervention (CBT *vs*. HyP) will be guaranteed. The different randomization steps (sequence generation and patient allocation) will be performed independently by the two investigators conducting the intervention sessions, who are aware of patients' allocated arm. Information concerning allocation is concealed from the investigator performing subsequent outcome assessment and from doctors and nurses involved in patients' care. There are no anticipated circumstances to justify unblinding of any parties for the duration of the trial, or discontinuation of intervention.

4. Intervention Groups

The two experimental conditions (CBT/HyP) have the same format of four consecutive weekly sessions of psychological intervention, scheduled following T0 assessment. Two doctorate-level health psychologists will conduct these groups individually, in a private and quiet room. Due to the nature of the interventions, each psychologist will perform only one type of intervention (CBT/HyP), based on training and expertise.

Specific scripts and manuals will be created for each intervention modality, based on theoretical and empirical foundations and taking into account the specificities of Haemophilia, its treatment and associated complications.

Strategies to promote participant retention and adherence to intervention and follow-up assessment sessions will include careful explanation of the study and expected benefits, session scheduling according to individual preferences and reminder telephone calls prior to intervention or assessment sessions. In order to control for co-intervention bias in the reported outcomes, all concomitant care (factor replacement consumption, analgesics and other medications, medical exams, physical therapy, ice, rest…) will be closely monitored, either by self-report and by collecting information from clinical records.

There are no anticipated adverse effects associated with the psychological interventions and/or assessment procedures, but their unlikely occurrence will be carefully monitored.

- *Experimental Group 1: Cognitive-Behavioral Therapy (CBT)*

According to this model, thoughts, beliefs, attributions and expectations play a key role in the perception of disease-related symptoms, such as pain, and in how people adjust to them.[63] The underlying process advocates a strong link between such cognitions and emotional state, physical symptoms and behaviors. Thus, alarming, self-defeating and unrealistic thoughts contribute to negative emotions and behavior (maladaptive coping responses) whilst realistic and more reassuring thoughts lead to more positive emotions and behavior (adaptive coping responses).[64,65]

Furthermore, CBT is a comprehensive approach and enables patients to integrate information on biological, psychological, and social influences about disease related-symptoms,[63] thereby enhancing their understanding on how the mind and body work together to influence the course of disease and the concomitant pain experience.

This protocol comprises four sessions, one educative and three focused on adaptive coping skills training, wherein active and structured techniques are taught, embracing coping with Haemophilia-specific threats, challenges and symptoms flare-ups (*e.g.* bleedings and pain), goal-setting, distraction, relaxation and problem-solving skills.

In this scope, the following contents and strategies will be approached: (1) educational rationale concerning the theoretical assumptions of CBT model, Haemophilia characteristics and pain experience (conceptualized as a multidimensional subjective experience, resulting from a dynamic and complex interaction among psychological, biological and social dimensions); (2) cognitive restructuring, with instruction and practice on the identification, challenging and replacing of negative and self-defeating automatic thoughts that may impact on Haemophilia symptoms, pain and psychological distress; (3) problem-solving skills, providing patients with an opportunity to deal with the constraints, consequences and implications of Haemophilia; and (4) relaxation techniques, coupled with attention diversion strategies.

Simultaneously, patients will be encouraged to work toward overall behavioural goals through homework assignments (e.g. keep a symptom diary to identify triggers of emotional distress or schedule daily pleasant activities).

- Experimental Groups 2: Hypnosis (HyP)

Hypnosis is a psychotherapeutic technique in which the person is guided by the hypnotist to respond to suggestions for alterations in subjective experience, such as changes in sensations, perceptions, emotions, cognitions or behaviors.[40,66] It includes elements such as relaxation, focused attention, imagery, interpersonal processing and suggestion.[67]

Hypnosis interventions usually comprise the following stages: introduction/preparation of the patient (explaining the rationale underlying Hypnosis, including dispelling potential myths, misconceptions and doubts); hypnotic induction (suggestions to promote a state of relaxation and focused awareness); imagery (*e.g.* imagining oneself as being in an agreeable and comfortable place); deepening procedure (further suggestions for achieving a more deeply relaxed and focused state); symptom-specific therapeutic suggestions (specific for each illness or disorder, aiming to change or improve symptoms and/or maladaptive behaviors) and conclusion.[40] Before concluding the process, posthypnotic suggestions might be made, to extend the benefits obtained beyond the session setting. In this line, providing patients with means to perform Hypnosis independently by themselves – self-hypnosis – assists in the reinforcement of those posthypnotic suggestions. Indeed, self-hypnosis constitutes a powerful resource that guarantees the practice of the technique, independently and in an autonomous fashion, thereby empowering patients and giving them a sense of control and mastery over their problems and their lives.[29,64]

Within this 4-sessions Hypnosis intervention, techniques will range from specific direct suggestions for symptom control following hypnotic induction, to a complex sequence of suggestions and metaphors for relaxation, guided imagery, ego strengthening, dissociation and well-being.

In order to engage patients in Hypnosis, the first step is to explain its principles, providing patients with a rationale for its learning and use. Moreover, and similarly to what occurs in CBT intervention, the explanation of Haemophilia characteristics and pain neurophysiology will be highlighted, emphasizing that pain results from a complex and dynamic interplay between biological processes and psychological factors (cognitive and emotional). Symptom-specific suggestions will address Haemophilia-specific challenges and threats, treatment-related difficulties, stress-producing situations, bleedings, pain and the emotional reactions to these symptoms, as well as Haemophilia adjustment. Specifically concerning pain, the hypnotic suggestions will focus on deep relaxation, sensory substitution, pain intensity reduction,

imagined anaesthesia and analgesia (skills for glove analgesia and transfer), decreased pain unpleasantness, managing breakthrough pain and post-hypnotic suggestions for effective self-Hypnosis.[65] All suggestions are made on a repetitive basis at each session and all sessions will end with post-hypnotic suggestions, underscoring that any experience of well-being, healing and comfort obtained will remain with the patient and last beyond the sessions, becoming a permanent part of how the patient lives life and cope with disease and problematic issues.

To promote the usage and customization of self-hypnosis, patients will also be given a CD of the session, and encouraged to practise self-hypnosis outside the sessions, at least on a daily basis.

Control group (CG)

Patients in the CG will receive medical treatments and standard care as usual. Assessments will be made in all the same five assessment time points as with EG participants, but without receiving any psychological intervention. At the end of the study, these patients will be given the opportunity to participate in four sessions of the intervention that would prove to be most effective at the end of this investigation.

5. Outcome Measures (see Table 1)

5.1. Primary Outcome Measures

Pain experience and Haemophilia-related QoL (A36Hemofilia-Qol), assessed after intervention (T1) and in the follow-up assessments of 3 (T2), 6 (T3) and 12 months (T4) after intervention ending.

5.2. Secondary Outcome Measures

- Clinical: factor replacement consumption (IU/kg per week), joint bleeding episodes and analgesic intake (type, dosage and frequency) assessed at T1, T2, T3 and T4.
- Psychological: pain coping strategies, anxiety, depression and illness perceptions, assessed at T1, T2, T3 and T4.
- Functional: assessment of the joints evaluated at T2 and T4.
- Physiological: inflammatory biomarkers - cytokines [pro-inflammatory (IL-1β, TNF-α, IL-6,) and anti-inflammatory (IL-10)], hs-CRP and white blood cells (WBC) count assessed at T2 and T4.

5.3. Other variables

- Sociodemographic (e.g. age, professional status) and clinical variables (e.g. inhibitor status, prophylaxis) will be taken into account as potential mediators or moderators for the influence of independent variables (type of intervention) on outcome measures.
- Hypnotic susceptibility will be assessed at baseline (T0) using the Stanford Hypnotic Susceptibility Scale.[68]

6. Data Collection

All data collection procedures (demographic, clinical, psychological and physiological) will be conducted by trained and experienced healthcare providers that are blinded to patient allocation. In order to avoid inter-assessor subjectivity, assessment of the joints will be performed by the same physician, an orthopedist with experience and training in Haemophilia care. To ensure the quality of self-reported data, the psychological assessment will be performed by the same investigator, a trained health psychologist experienced in psychological evaluation procedures. Blood samples will be collected by trained nurses.

6.1. Assessment Measures

Sociodemographic Information

- *Sociodemographic Questionnaire* (developed by the research team): collects patients' data concerning age, education, marital status, professional status, household, *etc*.

Clinical and Pain Assessment

- *Clinical Questionnaire* (developed by the research team): gathers general clinical information about patients' Haemophilia status, such as type and severity, age of diagnosis, type and frequency of medical treatments, factor replacement consumption, inhibitor status, joint bleeding episodes and comorbidities.
- *Multidimensional Haemophilia Pain Questionnaire* (developed by the research team): assesses Haemophilia related pain in terms of duration, frequency, location, impact, intensity, precipitating factors, treatment strategies, analgesic consumption and satisfaction with pain treatments, and was developed according to published guidelines for Haemophilia pain assessment.[9] This questionnaire intends to fill the gap in existing pain assessment tools for PWH[12] and is currently being used on the first Portuguese Haemophilia National Survey implemented by our team, in order to undergo a thorough validation process.

Psychological Assessment

The Portuguese versions of the following questionnaires will be used.

- *A36Hemofilia-QoL*:[69] Haemophilia-specific self-report questionnaire assessing health-related QoL. The 36 items are divided in nine subscales: Physical health; Daily activities; Joints; Pain; Treatment satisfaction; Treatment difficulties; Emotional functioning; Mental health; and Relationships and social activity. A total score can also be computed.

- *Hospital Anxiety and Depression Scale* (HADS):[70] assesses anxiety and depression in two separate subscales with 7 items each. Scoring in each item ranges from 0 to 3, with a total possible score varying from 0 to 21. Higher scores translate higher levels of anxiety and depression.

- *Coping Strategies Questionnaire-Revised Form* (CSQ-R):[71] includes 27 items that represent different coping strategies people usually recur to when in pain. It is organized in six subscales: Distraction/diverting attention; Praying and hoping; Ignoring pain sensations; Reinterpreting pain sensations; Pain-coping self-statements and Pain catastrophizing.

- *Illness Perception Questionnaire* (IPQ-R):[72] assesses patients beliefs about their illness, according to seven dimensions: Timeline acute/chronic; Timeline cyclical; Consequences; Personal control; Treatment control; Illness coherence; Emotional representation. In this study, participants will be evaluated with a shortened version of 21 items (3 items per subscale).[73]

Physiological Assessment

This will be performed through the collection of blood samples in order to conduct WBC count and to achieve a systemic evaluation of pro-inflammatory (IL-6, IL-1β, TNF-α) and anti-inflammatory cytokines (IL-10), as well as of hs-CRP.

Upon arrival at the Haemophilia Centre (between 9:30 am and 1:30 pm), patients will undergo sample blood collection and EDTA-samples will be transported immediately to the lab. In the lab, blood samples are centrifuged 15 minutes at 3.000 rpm, and plasma aliquoted and stored in a freezer at -70 ºC, until further analysis. Plasma levels of cytokines (IL-6, IL-1β, TNF-α, IL-10) are assayed in duplicate using ultra-sensitive multiplex human ELISA kits (Life Technologies®).

Functional Assessment

- *WFH Physical Examination Score (Gilbert Score):*[74] rates joint impairment based on clinical evaluation of joints, considering physical status evaluation and reported pain. Physical examination includes assessment of swelling, muscle atrophy, axial deformity, crepitus on motion, range of motion, flexion contracture and instability.

- *Pettersson Score*:[75] assesses joints quantitatively, based on the presence or absence of radiographic changes in eight dimensions: osteoporosis, enlargement of epiphysis, irregularity of subchondral surface, narrowing of joint space, subchondral cysts formation, erosion of joint margins, gross incongruence of articulating bone ends and joint deformity (angulation and/or displacement between articulating bones).

6.2. Data Analysis Plan

All data analysis procedures will be performed using IBM SPSS Statistics version 24 (SPSS Inc., Chicago, USA), except for sample size estimation, that will be calculated with G*Power 3.1.9, as described above.

The analysis plan will follow intention-to-treat principles (all participants as randomized). Frequencies and descriptive statistics (means, standard deviation, skewness and kurtosis) will be analyzed for sample characteristics at baseline and for outcome measures in the five assessment points. A mixed ANOVA will be performed to test mean differences between the three groups (CBT vs. HyP vs. CG; between-subject factor) over the five measurement points (within-subjects factor). This procedure allows the test of main group/intervention and time effects and mainly if there is a significant interaction effect between the two factors (between and the within subjects).

At the end of the study, it will be possible to determine if changes in outcomes (*e.g.* QoL) over time depend on the intervention. If no significant interaction effects are obtained, it can be concluded that changes in outcomes were simply due to time. Effect size measures (partial eta squared) and statistical power (1-β) will be presented for all statistical tests performed. Results will be considered significant for p-values < 0.05.

Since all data collection procedures will be conducted in-person, there is no anticipated missing data for baseline or subsequent assessments. In the case of missing values existence, missing value analysis will be performed to determine if missing observations are: a) completely at random (MCAR) or b) at random (MAR). Missing values replacement will be performed

accordingly (MCAR or MAR) using multiple imputation[76] performed using the IBM SPSS Amos v.24.

III. ETHICS AND DISSEMINATION

This investigation will submit to international ethical principles and guidelines for clinical studies involving humans. All participants will read and sign the informed consent and all doubts and questions will be addressed by the research team. Study-related data will be stored in locked cabinets and limited access, password protected computers, and confidentiality will be guaranteed by assigning a code to each participant. An anonymized final version of the dataset will be available to team members.

The study was authorized by the Portuguese National Data Protection Agency (CNPD) and approved by the Life Sciences and Health Ethics Subcommittee – University of Minho, and by the Centro Hospitalar de S. João – E.P.E. Ethics Committee. Any modification to the research protocol will be communicated in the clinicaltrials.gov RCT registry. Final conclusions of this investigation will be published in peer-reviewed journals and presented at Haemophilia international conferences, and made available to the PWH community through appropriate channels (national news channels, web and social media).

Authors' Contributions

PRP conceived the study idea and together with SP developed the design and created the intervention manuals. ACP and AA substantially contributed for the development and refinement of the study protocol. MC, ML and SF contributed for the refinement of the design with clinical expertise. PC supervised the power analyses and planned the data analysis. All authors participated in the drafting of this paper and critically revised and approved the final version. All authors are accountable for any issue regarding the accuracy and integrity of the work.

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Table 1. Time Assessment Points, Variables and Measures

		TIME ASSESSMENT POINTS				
VARIABLES	**MEASURES**	**T0** **Pre-test** Baseline Before intervention	**T1** **Post-test** After intervention	**T2** **Follow-up 1** 3 Months After Intervention	**T3** **Follow-up 2** 6 Months After Intervention	**T4** **Follow-up 3** 12 Months After Intervention
SOCIO-DEMOGRAPHICS VARIABLES	**Socio-demographic questionnaire**	**X**				
CLINICAL VARIABLES						
General clinical	**Clinical questionnaire**	**X**				
Pain	**Multidimensional Haemophilia Pain Questionnaire**	**X**	**X**	**X**	**X**	**X**
Analgesic intake	**Clinical questionnaire**	**X**	**X**	**X**	**X**	**X**
Factor Replacement Consumption	**Clinical questionnaire**	**X**	**X**	**X**	**X**	**X**
Joint Bleeding Episodes	**Clinical questionnaire**	**X**	**X**	**X**	**X**	**X**

		TIME ASSESSMENT POINTS				
VARIABLES	**MEASURES**	**T0** **Pre-test** Baseline Before intervention	**T1** **Post-test** After intervention	**T2** **Follow-up 1** 3 Months After Intervention	**T3** **Follow-up 2** 6 Months After Intervention	**T4** **Follow-up 3** 12 Months After Intervention
PSYCHOLOGICAL VARIABLES						
Anxiety and Depression	**HADS**	**X**	**X**	**X**	**X**	**X**
Coping Strategies	**CSQ-R**	**X**	**X**	**X**	**X**	**X**
QoL	**A36HemofiliaQol**	**X**	**X**	**X**	**X**	**X**
FUNCTIONAL VARIABLES						
Joint Orthopedic Status	**Pettersson Score & Gilbert Score**	**X**		**X**		**X**
PHYSIOLOGICAL VARIABLES						
Inflammatory Biomarkers	**Cytokines (IL-1β, IL-6, TNF-α, IL-10) & hs-CRP**	**X**		**X**		**X**
WBC Count		**X**		**X**		**X**

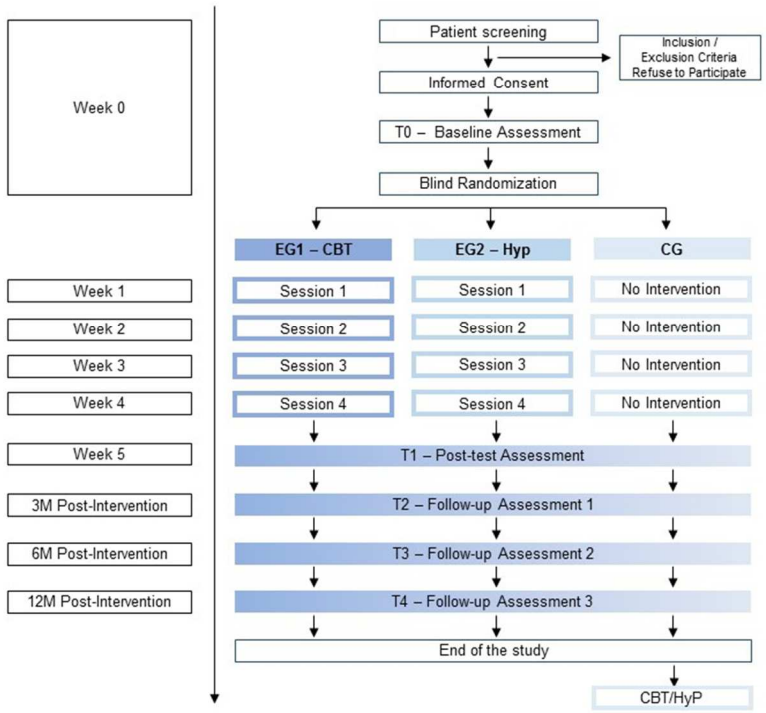

Figure 1. Trial design

Figure 1. Trial design

190x275mm (96 x 96 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1st version
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	3-6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12; Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7; Fig. 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A (Minimal risk RCT)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7, 12, 15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9, 11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effectiveness of two psychological interventions for pain management, emotional regulation and promotion of quality of life among adult Portuguese men with Haemophilia (PSY-HaEMOPEQ): study protocol for a single-center prospective randomized controlled trial

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Effectiveness of two psychological interventions for pain management, emotional regulation and promotion of quality of life among adult Portuguese men with Haemophilia (PSY-HaEMOPEQ): study protocol for a single-center prospective randomized controlled trial

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ABSTRACT

Introduction: Haemophilia is a bleeding disorder associated with significant pain, emotional distress, quality of life (QoL) impairment and considerable healthcare costs. Psychosocial health and effective pain management are considered essential endpoints for optimal haemophilia care, but there is a significant gap in evidence-based treatments targeting these outcomes in people with haemophilia (PWH). Psychological interventions are cost-effective in promoting emotional well-being, QoL and pain control, though these have been scarcely used in haemophilia field. This investigation aims to evaluate the effectiveness of two psychological interventions for pain management, emotional regulation and promotion of QoL in PWH.

Methods and Analysis: This is a single-center parallel randomized controlled trial conducted at a European Haemophilia Comprehensive Care Center in Portugal, with five assessment points: baseline (T0), post-intervention (T1), 3 (T2), 6 (T3) and 12 (T4) months follow-up. Eligible adult males, with moderate or severe haemophilia A or B will be randomized to experimental (EG) or control (CG) group. Intervention is either Cognitive-Behavioral Therapy (EG1) or Hypnosis (EG2), both consisting of four weekly sessions following standardized scripts delivered by trained psychologists. Randomization will be computer generated, allocation concealment will be guaranteed and outcome assessors will be blind to EG/CG allocation. Main outcomes are pain and haemophilia-related QoL and secondary outcomes include clinical (clotting factor replacement consumption, joint bleeding episodes, analgesic intake) and psychological (pain coping strategies, anxiety, depression, illness perceptions) variables, functional assessment of the joints, inflammatory biomarkers (cytokines, hs-CRP) and WBC count.

Ethics and dissemination: This study was approved by the competent authorities and all procedures will comply with international ethical guidelines for clinical studies involving humans. Written informed consent will be obtained from all participants. The dissemination plan includes peer-reviewed scientific publications, conference participation and web and media coverage.

Trial registration number: NCT02870452

Strengths and Limitations

- This is an innovative investigation, applying two empirically sound interventions (Cognitive-Behavioral Therapy and Hypnosis) to people with haemophilia.

- SPIRIT checklist guidelines were followed, to ensure quality in all aspects of study planning and execution.
- Random allocation and specific efforts to limit bias (blinded outcome assessment, standardization of intervention and collection of concomitant treatment) contribute to strengthen the study.
- Main limitation of this RCT is being a single-center study, limiting the generalizability of potential findings.

I. INTRODUCTION

1. Background and Rational

Haemophilia is an inherited X-linked bleeding disorder caused by a deficiency in coagulation factor VIII (haemophilia A) or IX (haemophilia B). Due to this deficit in coagulation factor, the main clinical manifestation of haemophilia is an increased bleeding tendency, either spontaneous or related to trauma or surgery. Spontaneous bleeding episodes occur mainly in the joints (hemarthrosis) and, if recurrent, lead to persistent joint damage and development of chronic joint arthropathy (hemophilic arthropathy).[1] Severity of haemophilia is classified according to clotting factor level, being defined as mild (clotting factor between 5%-40% of normal), moderate (1% to 5% of normal clotting factor) or severe (clotting factor level under 1% of normal), which generally correlates to a correspondent increase in bleeding frequency.[2]

Given the clinical presentation of haemophilia, the main goal of care is prevention and treatment of bleeds, which is mainly achieved through different modalities of clotting factor replacement therapy. However, recent guidelines have also highlighted the importance of considering psychosocial health and quality of life (QoL) as important outcomes for optimal care among people with haemophilia (PWH).[3,4] In fact, PWH have particular psychological and social needs related to haemophilia-specific threats and challenges, such as pain and daily living restrictions,[5] which impact significantly on QoL.[6] Therefore, the focus of current haemophilia management practice is not only to minimize joint disease but also to simultaneously increase QoL.[7]

In this context, a very relevant issue is pain, which is a common, highly debilitating feature of haemophilia that has been related with decreased QoL.[8] PWH experience acute pain during hemarthrosis, but might also report chronic pain resulting from hemophilic arthropathy.[1,9] On a recent 10 country survey, chronic pain related to haemophilia was reported by 38% of the

respondents, highlighting the high prevalence of this condition among PWH.[4] Nevertheless, patient reports also account for sub-optimal pain management, with 33 to 39% of patients in the United States and Europe reporting dissatisfaction with current pain treatment.[4,10-12] This question is such an important issue that, in an editorial, Humphries and Kessler[13] emphasize that the improvement of pain assessment, prevention and control is a key endpoint in the development of future treatments for PWH. In sum, pain control should be a priority in haemophilia treatment,[13] focusing not only on chronic pain management, but also on its prevention, as recommended by international guidelines, which state that non-pharmacological treatments, such as psychological interventions, should be considered for both these purposes.[8,10] However, despite well-established recommendations, there is still a scarcity of evidence-based treatment guidelines for haemophilia pain management. This is one important limitation to treatment progress in this field, justifying the need to conduct robust intervention-type investigations in this population.[8]

Another noteworthy issue is that psychological or psychiatric conditions are reported by 47% of PWH, with 29% relating these symptoms to haemophilia.[4] This is even more relevant considering that psychological factors can influence both pain experience and QoL in PWH.[12] Interestingly, Cassis and colleagues[6] state that variations in QoL are better explained by psychosocial, rather than clinical predictors. Since the former are potentially modifiable through psychological interventions, there is a recognized need to design interventions targeting social and psychological aspects of PWH.[14]

Indeed, psychological interventions have been proven to be effective in a broad range of disorders and illnesses.[15-18]Although a few former works have focused on psychological interventions in haemophilia, showing positive and promising results,[19-25] it is somewhat surprising the lack of recent papers exploring this issue, despite the recommendations and guidelines that emphasize their relevance. In those publications, a blend of psychological techniques was applied, with particular emphasis on hypnosis.[19,20,24,25] In fact, there is considerable evidence for the effectiveness of hypnosis as an empirically supported clinical intervention in managing symptoms such as pain,[26-35] and also in promoting psychological well-being across a variety of illnesses and disorders.[36-43] Among PWH, studies have shown that hypnosis can contribute not only to control pain, but also to reduce frequency and severity of bleedings and factor consumption.[19,20,24] Concurrently, by promoting better disease management, hypnosis can contribute to better coping and less distress.[24]

Besides hypnosis, cognitive-behavioral therapy is another psychological strategy commonly used in healthcare contexts. This has been the gold standard of psychological intervention, with recognized effectiveness in reducing negative emotions such as anxiety and depression, as well as in managing pain and promoting QoL in chronic disease.[15,17,44-48] Nevertheless, and to the best of our knowledge, it was never fully applied to haemophilia field.

In sum, and despite the shortage of studies focused on psychological interventions in haemophilia, these are recognized as complementary non-pharmacologic therapies and as a valuable resource to expand haemophilia care and potentially maximize treatment outcomes, promoting QoL and emotional well-being and improving symptoms management.[12,14]

Another relevant issue in the field of haemophilia concerns inflammatory biomarkers, such as cytokines and high-sensitivity C-reactive protein (hs-CRP), given their recognized role in inflammatory and degenerative processes that are related to the development of hemophilic arthropathy.[49] For instance, pro-inflammatory (*e.g.* IL-6, IL-1β, TNF-α) and anti-inflammatory (*e.g.* IL-10) cytokines have been implicated in the pathophysiology of hemophilic arthropathy, joint pain-associated nociceptive pathways and inhibitor development.[49-56] In addition, these biomarkers have also been shown to be correlates of psychological variables and, therefore, physiological approaches could support the potential efficacy of psychological interventions on disease and pain control.[57-59]

This is particularly relevant in light of the attention being given to psychosocial health in haemophilia, which has been advocated as a priority in the improvement of health status and QoL in PWH.[4,60] To this purpose, it is recommended that comprehensive care teams should be multidisciplinary and include a psychosocial expert, who can provide complete assessment of psychosocial status and contribute to an integrated disease management plan.[3] Globally, integrated care models are preferred over non-integrated care models, but there is still some uncertainty concerning which aspects of care might improve haemophilia management and patient outcomes, and what is the ideal composition of haemophilia care services.[61] Thus, there is an important gap between the need to clarify these issues and the lack of recent studies analyzing psychological interventions for PWH. This, added to the psychosocial impact of haemophilia discussed above, validates the need to advance research in this field, namely through the planning and implementation of clinical randomized controlled trials that test the effectiveness of distinct psychological interventions. In addition, it is noteworthy that, despite

pain being recognized as an important consequence of bleeding disorders, it has not been taken into account in most clinical trials of haemophilia.[13]

The current study protocol points to an innovative research that can contribute to better understand the impact and potential benefits of psychological interventions in haemophilia care setting. Given the negative impact of haemophilia on individual QoL and the associated healthcare costs, it is mandatory to evaluate the effectiveness of theoretically grounded psychological interventions in this field.

2. Objective

The primary objective of this study is to evaluate the relative effectiveness of two psychological interventions, Cognitive-Behavioral Therapy and Hypnosis, in order to manage pain, promote emotional regulation and improve QoL, among adult Portuguese men with Haemophilia.

II. METHODS

1. Trial Design

The design of this study follows the recommendations of Yates and colleagues[62] concerning psychological trials for pain, and reporting of the study results will follow CONSORT guidelines for trials of non-pharmacological interventions.[63]

This is a single-center three arm parallel prospective randomized controlled trial (RCT), with one control group (CG) and two experimental groups (EG): Cognitive-Behavioral Therapy (CBT) and Hypnosis (HyP), using an expertise-based RCT design. Participants in both groups will be followed longitudinally, in five time assessment points:

T0: Baseline assessment (pre-intervention, before randomization)

T1: Post-test assessment (1 week after intervention)

T2: Follow-up assessment 1 (3 months after intervention)

T3: Follow-up assessment 2 (6 months after intervention)

T4: Follow-up assessment 3 (12 months after intervention)

2. Participants and Procedures

According to sample size calculation, 66 patients will enter the study. Estimations were made using G*Power 3.1.9 and considering the following assumptions: to perform a one-way ANOVA

with fixed effects, large effect size (f =0.4), significance level (α – type I error) of 0.05 and statistical power (1-β – type II error) of 0.80.

Participants will be recruited at the European Haemophilia Comprehensive Care Center of São João Hospital Center, in Porto, Portugal. Eligible patients will be identified by the clinicians of the Haemophilia Centre and invited to participate if they comply with the following inclusion criteria:

a) Male gender;
b) Age ≥ 18;
c) Diagnosis of moderate or severe haemophilia A or B, with or without inhibitors;
d) Diagnostic of hemophilic arthropathy in at least one joint;
e) Chronic pain, as defined by the European Haemophilia Therapy Standardization Board (EHTSB);[10]
f) Ability to consent voluntary participation to the study;
g) Ability to read and write.

The exclusion criteria are:

a) Severe and debilitating neurologic conditions (e.g. dementia);
b) Severe psychiatric conditions (e.g. schizophrenia);
c) Currently undergoing any form of psychotherapy;
d) Unavailability to commit to four weekly sessions.

Patients willing to enroll will be screened by the clinicians to assess inclusion criteria and later referred to the investigators, who will describe and explain the study's objectives and interventions and clarify any concern or doubt, emphasizing confidentiality and voluntary nature of participation. After acceptance, patients sign the informed consent and baseline assessment is performed (T0). After baseline assessment, participants are randomly assigned to one of the three groups (CBT, HyP or CG) and, for patients in CBT and HyP groups, four weekly individual intervention sessions are scheduled. On the fifth week, all the patients are assessed for post-test assessment (T1). Follow-up assessments will take place at 3 (T2), 6 (T3) and 12 (T4) months after intervention ending for all participants (CBT, HyP and CG). Participant timeline for enrollment, intervention and assessment points is schematized in Figure 1.

3. Randomization and Allocation

Randomization procedures will follow a stratified blocked randomization process using a computerized random sequence generator. In order to control for potential confounding effects, stratification will be done by haemophilia severity. The generated sequence will be concealed and patient allocation will not be revealed until official enrollment, after consent is given and baseline assessment is completed. One of a series of consecutively numbered sealed opaque envelopes with group allocation will be opened at this moment and revealed to the patient. Due to obvious differences in procedure, blinding of the patients to intervention *vs*. control group is impossible. Moreover, it is possible that some patients are familiar with psychological intervention strategies and are able to recognize their allocated intervention and, therefore, blinding to type of psychological intervention (CBT *vs*. HyP) cannot be guaranteed. However, in order to prevent further bias, the type of intervention will not be disclosed to the patients. The different randomization steps (sequence generation and patient allocation) will be performed independently by the two investigators conducting the intervention sessions, who are aware of patients' allocated arm. Information concerning allocation is concealed from the investigator performing subsequent outcome assessment. There are no anticipated circumstances to justify unblinding of any parties for the duration of the trial, or discontinuation of intervention.

4. Intervention Groups

The two experimental conditions (CBT/HyP) have the same format of four consecutive weekly sessions of psychological intervention, scheduled following T0 assessment. Two doctorate-level health psychologists will conduct these groups individually, in a private and quiet room. Due to the nature of the interventions, each psychologist will perform only one type of intervention (CBT/HyP), based on training and expertise.

Specific scripts and manuals will be created for each intervention modality, based on theoretical and empirical foundations and taking into account the specificities of haemophilia, its treatment and associated complications.

Strategies to promote participant retention and adherence to intervention and follow-up assessment sessions will include careful explanation of the study and expected benefits, session scheduling according to individual preferences and reminder telephone calls prior to intervention or assessment sessions. In order to control for co-intervention bias in the reported outcomes, all concomitant care (clotting factor replacement consumption, analgesics and other

medications, medical exams, physical therapy, ice, rest…) will be closely monitored, either by self-report or by collecting information from clinical records.

There are no anticipated adverse effects associated with the psychological interventions and/or assessment procedures, but their unlikely occurrence will be carefully monitored.

- *Experimental Group 1: Cognitive-Behavioral Therapy (CBT)*

According to this model, thoughts, beliefs, attributions and expectations play a key role in the perception of disease-related symptoms, such as pain, and in how people adjust to them.[64] The underlying process advocates a strong link between such cognitions and emotional state, physical symptoms and behaviors. Thus, alarming, self-defeating and unrealistic thoughts contribute to negative emotions and behavior (maladaptive coping responses) whilst realistic and more reassuring thoughts lead to more positive emotions and behavior (adaptive coping responses).[65,66]

Furthermore, CBT is a comprehensive approach and enables patients to integrate information on biological, psychological, and social influences about disease related-symptoms,[64] thereby enhancing their understanding on how the mind and body work together to influence the course of disease and the concomitant pain experience.

This protocol comprises four sessions, one educative and three focused on adaptive coping skills training, wherein active and structured techniques are taught, embracing coping with haemophilia-specific threats, challenges and symptoms flare-ups (*e.g.* bleedings and pain), goal-setting, distraction, relaxation and problem-solving skills.

In this scope, the following contents and strategies will be approached: (1) educational rationale concerning the theoretical assumptions of CBT model, haemophilia characteristics and pain experience (conceptualized as a multidimensional subjective experience, resulting from a dynamic and complex interaction among psychological, biological and social dimensions); (2) cognitive restructuring, with instruction and practice on the identification, challenging and replacing of negative and self-defeating automatic thoughts that may impact on haemophilia symptoms, pain and psychological distress; (3) problem-solving skills, providing patients with an opportunity to deal with the constraints, consequences and implications of haemophilia; and (4) relaxation techniques, coupled with attention diversion strategies.

Simultaneously, patients will be encouraged to work toward overall behavioural goals through homework assignments (e.g. keep a symptom diary to identify triggers of emotional distress or schedule daily pleasant activities).

- *Experimental Groups 2: Hypnosis (HyP)*

Hypnosis is a psychotherapeutic technique in which the person is guided by the hypnotist to respond to suggestions for alterations in subjective experience, such as changes in sensations, perceptions, emotions, cognitions or behaviors.[41,67] It includes elements such as relaxation, focused attention, imagery, interpersonal processing and suggestion.[68]

Hypnosis interventions usually comprise the following stages: introduction/preparation of the patient (explaining the rationale underlying hypnosis, including dispelling potential myths, misconceptions and doubts); hypnotic induction (suggestions to promote a state of relaxation and focused awareness); imagery (*e.g.* imagining oneself as being in an agreeable and comfortable place); deepening procedure (further suggestions for achieving a more deeply relaxed and focused state); symptom-specific therapeutic suggestions (specific for each illness or disorder, aiming to change or improve symptoms and/or maladaptive behaviors) and conclusion.[41] Before concluding the process, posthypnotic suggestions might be made, to extend the benefits obtained beyond the session setting. In this line, providing patients with means to perform hypnosis independently by themselves – self-hypnosis – assists in the reinforcement of those posthypnotic suggestions. Indeed, self-hypnosis constitutes a powerful resource that guarantees the practice of the technique, independently and in an autonomous fashion, thereby empowering patients and giving them a sense of control and mastery over their problems and their lives.[30,65]

Within this 4-sessions hypnosis intervention, techniques will range from specific direct suggestions for symptom control following hypnotic induction, to a complex sequence of suggestions and metaphors for relaxation, guided imagery, ego strengthening, dissociation and well-being.

In order to engage patients in hypnosis, the first step is to explain its principles, providing patients with a rationale for its learning and use. Moreover, and similarly to what occurs in CBT intervention, the explanation of haemophilia characteristics and pain neurophysiology will be highlighted, emphasizing that pain results from a complex and dynamic interplay between biological processes and psychological factors (cognitive and emotional). Symptom-specific

suggestions will address haemophilia-specific challenges and threats, treatment-related difficulties, stress-producing situations, bleedings, pain and the emotional reactions to these symptoms, as well as haemophilia adjustment. Specifically concerning pain, the hypnotic suggestions will focus on deep relaxation, sensory substitution, pain intensity reduction, imagined anaesthesia and analgesia (skills for glove analgesia and transfer), decreased pain unpleasantness, managing breakthrough pain and post-hypnotic suggestions for effective self-hypnosis.[66] All suggestions are made on a repetitive basis at each session and all sessions will end with post-hypnotic suggestions, underscoring that any experience of well-being, healing and comfort obtained will remain with the patient and last beyond the sessions, becoming a permanent part of how the patient lives life and cope with disease and problematic issues.

To promote the usage and customization of self-hypnosis, patients will also be given a CD of the session, and encouraged to practise self-hypnosis outside the sessions, at least on a daily basis.

Control group (CG)

Patients in the CG will receive medical treatments and standard care as usual. Assessments will be made in all the same five assessment time points as with EG participants, but without receiving any psychological intervention. At the end of the study, these patients will be given the opportunity to participate in four sessions of the intervention that would prove to be most effective at the end of this investigation.

5. Outcome Measures (see Table 1)

5.1. Primary Outcome Measures

Pain experience (frequency, intensity and interference) and haemophilia-related QoL, assessed after intervention (T1) and in the follow-up assessments of 3 (T2), 6 (T3) and 12 months (T4) after intervention ending.

5.2. Secondary Outcome Measures

- Clinical: clotting factor replacement consumption (IU/kg per week), joint bleeding episodes and analgesic intake (type, dosage and frequency) assessed at T1, T2, T3 and T4.
- Psychological: anxiety, depression, pain coping strategies and illness perceptions, assessed at T1, T2, T3 and T4.
- Functional: assessment of the joints evaluated at T2 and T4.

- Physiological: inflammatory biomarkers - cytokines [pro-inflammatory (IL-1β, TNF-α, IL-6,) and anti-inflammatory (IL-10)], hs-CRP and white blood cells (WBC) count assessed at T2 and T4.

5.3. Other variables

- Sociodemographic (e.g. age, professional status) and clinical variables (e.g. inhibitor status, prophylaxis) will be taken into account as potential mediators or moderators for the influence of independent variables (type of intervention) on outcome measures.

- Hypnotic susceptibility will be assessed in all patients at baseline (T0) using the Stanford Hypnotic Susceptibility Scale.[69]

6. Data Collection

All data collection procedures (demographic, clinical, psychological and physiological) will be conducted by trained and experienced healthcare providers. In order to avoid inter-assessor subjectivity, assessment of the joints will be performed by the same physician, an orthopedist with experience and training in haemophilia care. To ensure the quality of self-reported data, the psychological assessment will be performed by the same investigator, a trained health psychologist experienced in psychological evaluation procedures. Blood samples will be collected by trained nurses.

6.1. Assessment Measures

Sociodemographic Information

- *Sociodemographic Questionnaire* (developed by the research team): collects patients' data concerning age, education, marital status, professional status, household, *etc*.

Clinical and Pain Assessment

- *Clinical Questionnaire* (developed by the research team): gathers general clinical information about patients' haemophilia status, such as type and severity, age at time of diagnosis, type and frequency of medical treatments, clotting factor replacement consumption, inhibitor status, joint bleeding episodes and comorbidities.

- *Multidimensional Haemophilia Pain Questionnaire* (MHPQ)*:* developed by the research team to assess haemophilia-related pain, following published guidelines for haemophilia pain assessment[10] and intending to fill a gap in existing pain assessment tools for PWH.[13]

Questionnaire development was based on an extensive literature review, expert opinion, pilot studying and further refinement of item content and wording. It is currently going through the validation process, after being used in its experimental version on the first Portuguese haemophilia national survey conducted by our team.

The MHPQ has 26 items regarding haemophilia-related pain experienced in the previous year. Four items assess the presence of chronic pain according to the EHTSB guidelines, defined as continuous and/or intermittent pain, related to the pathophysiology of haemophilia and requiring pharmacological or non-pharmacological intervention, in which the cause of pain cannot be readily removed, that occurs more than once a week and lasts 3 months or more.[10]

The remaining questions are divided in nine dimensions:

Painful locations: asks about haemophilia-related pain locations, specifying the most painful location and the one which caused the greatest impact.

Duration: assesses how long ago the pain with greatest impact started.

Frequency: evaluates how often the pain is present and when was the last time it occurred.

Triggering factors (and temporal pattern): requires the selection, from a list, of haemophilia pain potential triggers, such as: bleeds, climbing stairs or weather changes, specifying the daytime when pain is most often experienced.

Intensity: measured in regard to specific situations, such as during bleeds, while in rest or during movement, through a 0-10 Numerical Rating Scale (NRS) (0=no pain; 10=worst imaginable pain).

Interference: these items were drawn from the Brief Pain Inventory's interference subscale,[70] evaluating pain interference with general activity, mood, walking ability, normal work, relations with people, sleep and enjoyment of life, assessed according to a NRS (0=no interference; 10=completely interferes).

Strategies for pain control: several strategies are presented (factor replacement, rest, ice, analgesics, distracting, …) for people to mark the ones they usually do or ever did and the degree of relief they provide (0%-100% scale).

Pain management specialists: asks about pain specialists people have or would like to consult to help manage pain (e.g.: haemophilia doctors, anesthesiologists, psychologists, professionals of alternative therapies, …).

Satisfaction with pain treatment: evaluates global satisfaction with pain treatment through a single question, on a 5-point scale (ranging from 1="very dissatisfied" to 5="very satisfied").

Each dimension in analyzed separately and no global pain score is computed for the MHPQ.

Psychological Assessment

The Portuguese versions of the following questionnaires will be used.

- *A36Hemofilia-Qol*:[71] this is an haemophilia-specific self-report questionnaire assessing health-related QoL. The 36 items are divided in nine subscales: physical health; daily activities; joints; pain; treatment satisfaction; treatment difficulties; emotional functioning; mental health; and relationships and social activity. A total score can also be computed. The A36-Hemofilia-Qol was originally developed and validated in Spain with good validity and reliability properties.[71] The Portuguese version was created following a complete translation back-translation process by certified translators. Similarly to the abovementioned MHPQ, it is currently going through the validation process.

- *Hospital Anxiety and Depression Scale* (HADS):[72] assesses anxiety and depression in two separate subscales with 7 items each. Scoring in each item ranges from 0 to 3, with a total possible score varying from 0 to 21. Higher scores translate higher levels of anxiety and depression. This questionnaire was developed in a hospital outpatient clinic, avoiding questions that could be influenced by physical illness symptoms[72] and has since been found a reliable measure of anxiety and depression symptom severity in physical and psychiatric illness, primary care patients and general population.[73] It has been validated for Portuguese patients.[74]

- *Coping Strategies Questionnaire-Revised Form* (CSQ-R):[75] includes 27 items that represent different coping strategies people usually use when in pain. It is organized in six subscales: distraction/diverting attention; praying and hoping; ignoring pain sensations; reinterpreting pain sensations; pain-coping self-statements and pain catastrophizing. The Portuguese version applied in this study has been used in several investigations in hospital setting with good reliability properties.[76-78]

- *Illness Perception Questionnaire* (IPQ-R):[79] assesses patients beliefs about their illness, according to seven dimensions: timeline acute/chronic; timeline cyclical; consequences; personal control; treatment control; illness coherence; emotional representation. The IPQ-R has been validated for Portugal[80] and, in this study, participants will be evaluated with a psychometrically shortened version of 21 items,[81] previously used in Portuguese clinical setting,[76-78] to reduce respondent burden.

Physiological Assessment

This will be performed through the collection of blood samples in order to conduct WBC count and to achieve a systemic evaluation of pro-inflammatory (IL-6, IL-1β, TNF-α) and anti-inflammatory cytokines (IL-10), as well as of hs-CRP.

Upon arrival at the Haemophilia Centre (between 9:30 am and 1:30 pm), patients will undergo sample blood collection and EDTA-samples will be transported immediately to the lab. In the lab, blood samples are centrifuged 15 minutes at 3.000 rpm, and plasma aliquoted and stored in a freezer at -70 ºC, until further analysis. Plasma levels of cytokines (IL-6, IL-1β, TNF-α, IL-10) are assayed in duplicate using ultra-sensitive multiplex human ELISA kits (Life Technologies®).

Functional Assessment

- *WFH Physical Examination Score (Gilbert Score):*[82] rates joint impairment based on clinical evaluation of joints, considering physical status evaluation and reported pain. Physical examination includes assessment of swelling, muscle atrophy, axial deformity, crepitus on motion, range of motion, flexion contracture and instability.

- *Pettersson Score*:[83] assesses joints quantitatively, based on the presence or absence of radiographic changes in eight dimensions: osteoporosis, enlargement of epiphysis, irregularity of subchondral surface, narrowing of joint space, subchondral cysts formation, erosion of joint margins, gross incongruence of articulating bone ends and joint deformity (angulation and/or displacement between articulating bones).

6.2. Data Analysis Plan

All data analysis procedures will be performed using IBM SPSS Statistics version 24 (SPSS Inc., Chicago, USA), except for sample size estimation, that will be calculated with G*Power 3.1.9, as described above.

The analysis plan will follow intention-to-treat principles (all participants as randomized). Frequencies and descriptive statistics (means, standard deviation, skewness and kurtosis) will be analyzed for sample characteristics at baseline and for outcome measures in the five assessment points. A mixed ANOVA will be performed to test mean differences between the three groups (CBT vs. HyP vs. CG; between-subject factor) over the five measurement points (within-subjects factor). This procedure allows the test of main group/intervention and time

effects and mainly if there is a significant interaction effect between the two factors (between and the within subjects).

At the end of the study, it will be possible to determine if changes in outcomes (*e.g.* QoL) over time depend on the intervention. If no significant interaction effects are obtained, it can be concluded that changes in outcomes were simply due to time. Effect size measures (partial eta squared) and statistical power (1-β) will be presented for all statistical tests performed. Results will be considered significant for p-values < 0.05.

Since all data collection procedures will be conducted in-person, there is no anticipated missing data for baseline or subsequent assessments. In the case of missing values existence, missing value analysis will be performed to determine if missing observations are: a) completely at random (MCAR) or b) at random (MAR). Missing values replacement will be performed accordingly (MCAR or MAR) using multiple imputation[84] performed using the IBM SPSS Amos v.24.

III. ETHICS AND DISSEMINATION

This investigation will submit to international ethical principles and guidelines for clinical studies involving humans. All participants will read and sign the informed consent and all doubts and questions will be addressed by the research team. Study-related data will be stored in locked cabinets and limited access, password protected computers, and confidentiality will be guaranteed by assigning a code to each participant. An anonymized final version of the dataset will be available to team members.

The study was authorized by the Portuguese National Data Protection Agency (CNPD) and approved by the Life Sciences and Health Ethics Subcommittee – University of Minho, and by the Centro Hospitalar de S. João – E.P.E. Ethics Committee. Any modification to the research protocol will be communicated in the clinicaltrials.gov RCT registry. Final conclusions of this investigation will be published in peer-reviewed journals and presented at haemophilia international conferences, and made available to the PWH community through appropriate channels (national news channels, web and social media).

Authors' Contributions

PRP conceived the study idea and together with SP developed the design and created the intervention manuals. ACP and AA substantially contributed for the development and

refinement of the study protocol. MC, ML and SF contributed for the refinement of the design with clinical expertise. PC supervised the power analyses and planned the data analysis. All authors participated in the drafting of this paper and critically revised and approved the final version. All authors are accountable for any issue regarding the accuracy and integrity of the work.

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Figure 1. Trial design

Table 1. Time Assessment Points, Variables and Measures

		TIME ASSESSMENT POINTS				
VARIABLES	**MEASURES**	**T0** **Pre-test** Baseline Before intervention	**T1** **Post-test** After intervention	**T2** **Follow-up 1** 3 Months After Intervention	**T3** **Follow-up 2** 6 Months After Intervention	**T4** **Follow-up 3** 12 Months After Intervention
SOCIO-DEMOGRAPHICS VARIABLES	**Socio-demographic questionnaire**	**X**				
HYPNOTIC SUSCEPTIBILITY	**SHSS:C**	**X**				
CLINICAL VARIABLES						
General clinical	**Clinical questionnaire**	**X**				
Pain	**Multidimensional Haemophilia Pain Questionnaire**	**X**	**X**	**X**	**X**	**X**
Analgesic intake	**Clinical questionnaire**	**X**	**X**	**X**	**X**	**X**
Clotting Factor Replacement Consumption	**Clinical questionnaire**	**X**	**X**	**X**	**X**	**X**
Joint Bleeding Episodes	**Clinical questionnaire**	**X**	**X**	**X**	**X**	**X**

VARIABLES	MEASURES	T0 **Pre-test** Baseline Before intervention	T1 **Post-test** After intervention	T2 **Follow-up 1** 3 Months After Intervention	T3 **Follow-up 2** 6 Months After Intervention	T4 **Follow-up 3** 12 Months After Intervention
PSYCHOLOGICAL VARIABLES						
Anxiety and Depression	**HADS**	**X**	**X**	**X**	**X**	**X**
Coping Strategies	**CSQ-R**	**X**	**X**	**X**	**X**	**X**
QoL	**A36HemofiliaQol**	**X**	**X**	**X**	**X**	**X**
Illness Perception	**IPQ-R**	**X**	**X**	**X**	**X**	**X**
FUNCTIONAL VARIABLES						
Joint Orthopedic Status	**Pettersson Score & Gilbert Score**	**X**		**X**		**X**
PHYSIOLOGICAL VARIABLES						
Inflammatory Biomarkers	**Cytokines (IL-1β, IL-6, TNF-α, IL-10) & hs-CRP**	**X**		**X**		**X**
WBC Count		**X**		**X**		**X**

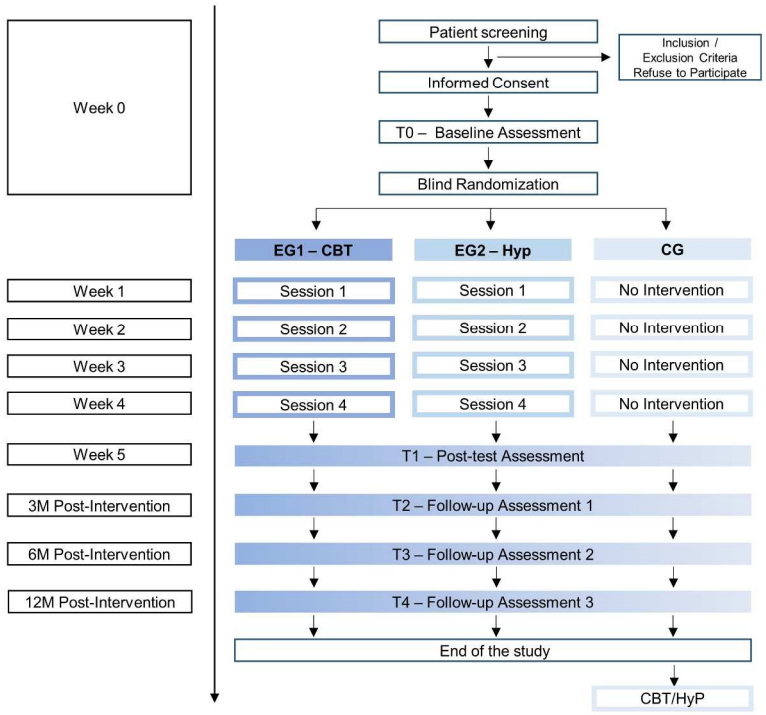

Figure 1. Trial design

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1st version
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-6
	6b	Explanation for choice of comparators	3-6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12; Table 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7; Fig. 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6-7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A (Minimal risk RCT)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7, 12, 15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9, 11
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.